

response. For example, a hypoxic induction assay may be performed on cells that over- or under-express MELK relative to wild type cells. Differences in hypoxic response compared to wild type cells ~~suggests~~ suggest that the MELK plays a direct role in hypoxic induction.

Change(s) applied
to document,
/K.W./
10/20/2011

Please replace the fourth paragraph on page ^{seven} ~~twenty-eight~~ of the specification with the following substitute paragraph:

Tubulogenesis. Tubulogenesis assays monitor the ability of cultured cells, generally endothelial cells, to form tubular structures on a matrix substrate, which generally simulates the environment of the extracellular matrix. Exemplary substrates include Matrigel MATRIGELTM (Becton Dickinson), an extract of basement membrane proteins containing laminin, collagen IV, and heparin sulfate proteoglycan, which is liquid at 4° C and forms a solid gel at 37° C. Other suitable matrices comprise extracellular components such as collagen, fibronectin, and/or fibrin. Cells are stimulated with a pro-angiogenic stimulant, and their ability to form tubules is detected by imaging. Tubules can generally be detected after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Tube formation assays are well known in the art (e.g., Jones MK et al., 1999, Nature Medicine 5:1418-1423). These assays have traditionally involved stimulation with serum or with the growth factors FGF or VEGF. Serum represents an undefined source of growth factors. In a preferred embodiment, the assay is performed with cells cultured in serum free medium, in order to control which process or pathway a candidate agent modulates. Moreover, we have found that different target genes respond differently to stimulation with different pro-angiogenic agents, including inflammatory angiogenic factors such as TNF-~~alpha~~ alpha. Thus, in a further preferred embodiment, a tubulogenesis assay system comprises testing a MELK's response to a variety of factors, such as FGF, VEGF, phorbol myristate acetate (PMA), TNF-alpha, ephrin, etc.

Please replace the second paragraph on page twenty-nine of the specification with the following substitute paragraph:

For antibody modulators, appropriate primary assays test is a binding assay that tests the antibody's affinity to and specificity for the MELK protein. Methods for testing antibody affinity and specificity are well known in the art (Harlow and Lane, 1988, 1999,